An analysis of reports of depression and suicide in patients treated with isotretinoin

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Background: The Food and Drug Administration (FDA) has received reports of depression and suicide in patients treated with isotretinoin.

Objective: Our purpose was to provide the number and describe the cases of depression and suicide reported to the FDA in US patients treated with isotretinoin and to consider the nature of a possible association between isotretinoin and depression.

Methods: An analysis was made of reports of depression, suicidal ideation, suicide attempt, and suicide in US isotretinoin users voluntarily submitted to the manufacturer and the FDA from 1982 to May 2000 and entered in the FDA's Adverse Event Reporting System database.

Results: From marketing of isotretinoin in 1982 to May 2000, the FDA received reports of 37 US patients treated with isotretinoin who committed suicide; 110 who were hospitalized for depression, suicidal ideation, or suicide attempt; and 284 with nonhospitalized depression, for a total of 431 patients. Factors suggesting a possible association between isotretinoin and depression include a temporal association between use of the drug and depression, positive dechallenges (often with psychiatric treatment), positive rechallenges, and possible biologic plausibility. Compared with all drugs in the FDA's Adverse Event Reporting System database to June 2000, isotretinoin ranked within the top 10 for number of reports of depression and suicide attempt.

Conclusion: The FDA has received reports of depression, suicidal ideation, suicide attempt, and suicide in patients treated with isotretinoin. Additional studies are needed to determine whether isotretinoin causes depression and to identify susceptible persons. In the meantime, physicians are advised to inform patients prescribed isotretinoin (and parents, if appropriate) of the possibility of development or worsening of depression. They should advise patients (and parents) to immediately report mood swings and symptoms suggestive of depression such as sadness, crying, loss of appetite, unusual fatigue, withdrawal, and inability to concentrate so that patients can be promptly evaluated for appropriate treatment, including consideration of drug discontinuation and referral for psychiatric care. (J Am Acad Dermatol 2001;45:515-9.)

Isotretinoin (13-*cis*-retinoic acid, Accutane, Roche Pharmaceuticals, Nutley, NJ) was approved in the United States in 1982 as treatment for severe recalcitrant nodular acne. The drug is a retinoid, a derivative of vitamin A, and the 13-*cis* isomer of all-*trans*-retinoic acid (tretinoin). Isotretinoin is a known human teratogen, and numerous side effects including dry mucous membranes, headache, alopecia, hypertriglyceridemia, and joint and muscle pain have been reported to the Food and Drug Administration (FDA). The FDA also has received reports of psychiatric adverse events, most notably depression and suicide, in patients treated with isotretinoin. As a result, in February 1998 the manufacturer sent Dear Health Professional letters to alert physicians about a new warning in the approved labeling: "Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events."

Since this warning, additional reports of depression and suicide in isotretinoin users have been

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Conflict of Interest: None.

The views expressed are those of the authors and do not necessarily represent the official position of the Food and Drug Administration.

Accepted for publication May 21, 2001.
Reprints not available from authors.

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16/1/117730
doi:10.1067/mjd.2001.117730

received.[1] To seek guidance regarding risk management of psychiatric events in patients treated with isotretinoin, the FDA convened a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee in September 2000. The FDA's data and the Committee's recommendations are presented herein.

METHODS

The Office of Post-Marketing Drug Risk Assessment of the FDA receives reports of adverse drug events primarily from physicians and pharmacists who submit them on a standardized form directly to the FDA or indirectly through pharmaceutical companies. Reports are entered into a computerized database, the Adverse Event Reporting System (AERS) using a coding thesaurus of adverse reaction terms used for searching and retrieval purposes. From 1969 through September 2000, more than 2 million reports of adverse events for marketed drugs have been entered.

We reviewed and analyzed domestic reports with isotretinoin as the suspect drug and having codes of depression, dysthymic disorder, major depressive disorder, aggravated depression, and suicidal depression that were entered into the AERS database from marketing of isotretinoin to early May 2000. Initial and follow-up reports for the same patients were paired and duplicates were excluded. Also excluded were reports of hospitalized patients for whom depression was not the primary reason for hospitalization. We analyzed reports by demographic factors of patients and focused on possible risk factors for depression and suicide. We also compared the rank for isotretinoin in number of reports of depression with all other drugs in the AERS database.

RESULTS

In the 18-year period from marketing of isotretinoin to May 2000, the FDA received reports of depression, suicidal ideation, suicide attempts, and completed suicide for 431 exposed patients. Data describing these patients are given in the following paragraphs.

Suicides

Thirty-seven US patients were reported to have committed suicide, 24 while using and 13 after stopping isotretinoin. Thirty-one (84%) of the 37 persons were male and the median age was 17 years (range, 13-32 years). Seventeen (46%) were being treated for cystic acne, 5 (14%) for "severe acne" or another skin condition, 10 (27%) for "acne," and 5 for an unspecified condition.

Median time while using or after stopping the drug to suicide was 3 months and 2.5 months, respectively. Psychiatric history was reported for 8 (22%); 21 (57%) had other possible contributing factors (eg, personal relationship problems, stressful life events, alcohol use, family history of psychiatric disorders). Together, 62% were reported to have either a psychiatric history or possible contributing factors. The median peak dose was 1 mg/kg per day (range, 0.6-1.7 mg/kg/d), which is within the US recommended dose range for isotretinoin of 0.5 to 2 mg/kg per day. About 49% of the reports were received in 1998—after suicide and depression were added as a warning to the product labeling in February of that year.

Hospitalizations

One hundred ten US patients were reported as having been hospitalized for depression, suicide ideation, and suicide attempt, 85 while using and 25 after stopping isotretinoin. Sixty-two (56%) were female; the median age was 17 years (range, 12-47 years). Fifty-six patients (51%) were being treated for cystic acne, 11 (10%) for severe acne or other condition, 32 (29%) for "acne," and 11 for an unspecified disorder. Median time while using or after stopping the drug to hospitalization was 1 month and 3 months, respectively. Psychiatric history was reported for 48 (44%) of the 110 patients, and other possible contributing factors were reported for 57 (52%). Together, 76 (69%) had either a previous psychiatric history or possible contributing factors. The median peak dose was 1.1 mg/kg per day (range, 0.5-2.5 mg/kg/d). For about one third of hospitalized patients, improvement occurred with drug discontinuation and psychiatric treatment, but depression persisted (despite acne improvement for most persons) after drug discontinuation for approximately 29%. Four patients were rechallenged; symptoms redeveloped in one, and 3 were able to continue the drug with dose reduction, alcohol abstinence, or continued use of an antidepressant. For most of the remaining patients, isotretinoin was not discontinued or the outcome was unknown.

Nonhospitalized patients

An additional 284 patients were reported to the FDA with diagnoses of depression, of whom 149 (52%) had accompanying side effects such as dry mucous membranes, headache, alopecia, joint and muscle pain, hypertriglyceridemia, and others. Twenty-four persons (including the two described below) had positive rechallenges. Forty-five percent of reports were received in 1998 after the addition of the warning concerning suicide and depression.

About half the reports of nonhospitalized patients were submitted from consumers and relatives, a higher proportion compared with reports for most drugs in AERS.

Selected positive rechallenge reports

A 19-year-old man started an unknown dose of isotretinoin for treatment of cystic acne. During the patient's first course of therapy (of 3-4 months) he experienced personality changes, mood swings, and depression. After completing therapy, he returned to normal. The patient started a second course of isotretinoin at an unknown date. Again, he experienced personality changes, mood swings, and depression, but returned to normal after completing the 3- to 4-month course of therapy. Sometime later, the patient started a third course of isotretinoin. This time the personality changes, mood swings, and depression recurred and persisted after completion of the 3- to 4-month course. About a year after the third course, the patient was referred for counseling. Before isotretinoin treatment his medical history was "uneventful" and his personality was "cheerful." No concomitant medications were reported.

An 18-year-old man receiving no other medications and without a reported relevant medical history started isotretinoin, 1.1 mg/kg per day (40 mg twice daily), for cystic acne. Twenty-nine days later, he experienced depression, loss of interest in daily activities, and decreased school performance. Isotretinoin was discontinued. The symptoms cleared in 8 days. Isotretinoin was restarted at 0.5 mg/kg per day (40 mg daily). Five days after restarting the drug, the patient again experienced depression, loss of interest in activities, and decreased school performance. Isotretinoin was again discontinued, and the symptoms cleared in 7 days. At an unknown date, it was restarted at 40 mg weekly, without a recurrence of symptoms.

Comparison with other drugs for reports of depression

Compared with all drugs in the AERS database to June 2000, isotretinoin ranked number 4 and 5 in number of reports of depression and serious depression, respectively, and 10th in number of reports of suicide attempt. (Most of the drugs with top ranks have known psychoactive properties and psychiatric indications; in fact, isotretinoin was the only drug with a nonpsychiatric indication in the top 10 ranked drugs for suicide attempt.) A statistical data-mining analysis of all adverse events and drug combinations in the AERS database determined that 6 reports of suicide were expected for isotretinoin compared with the 37 suicides observed.[2,3]

Compared with all adverse events reported for isotretinoin, depression was near the top of the list, ranking number 6.

DISCUSSION

There are several pieces of evidence that suggest a possible causal association between depression and isotretinoin. These include the relatively large number of reports of serious depression submitted to the FDA for isotretinoin; the temporal relationship between use of the drug and the onset, or worsening, of depression; positive dechallenges with isotretinoin discontinuation and initiation of psychiatric treatment; and positive rechallenges. In addition, the relationship between use of retinoids (including isotretinoin) and depression may be biologically plausible.

Psychiatric adverse events have been linked with high-dose vitamin A (retinol) and etretinate, a systemic retinoid indicated for treatment of severe psoriasis. In 1972, Restak[4] described the development of a severe neuropsychiatric reaction to long-term use of high-dose vitamin A initiated 6 months earlier in an 18-year-old acne patient without antecedent psychiatric illness. Severe depression preceded by a year the development of pseudotumor cerebri, a well-known adverse effect of the synthetic retinoids.[5] Resolution of both effects occurred rapidly upon discontinuation of vitamin A. Depression linked to the aromatic retinoid etretinate has also been reported.[6-8]

Studies in mice and rats indicate that retinoids enter the central nervous system and their receptors are present in the adult brain.[9-12] A recently published study reported that administration of all-*trans*-retinoic acid (a metabolite of isotretinoin) to rats resulted in peak cerebral white matter levels that were 6 to 7 times higher than peak serum levels.[11] Animal studies also suggest a relationship between retinoids and adult neuronal pathways believed to be involved in mood and thought disorders.[12]

Case reports and studies of isotretinoin and depression[13-20] have been published. In 1983, Hazen et al[13] reported depressive symptoms in 6 (5.5%) of 110 patients treated with isotretinoin, 1 to 2 mg/kg per day; symptoms resolved rapidly with discontinuation of therapy. Scheinman et al[14] reported that 7 (1%) of 700 patients treated with isotretinoin in clinical trials of cystic acne, psoriasis, cutaneous disorders of keratinization, or basal cell carcinoma spontaneously reported major depressive symptoms. The onset was not related to dosage or time, and all depressive symptoms rapidly resolved within 1 week of drug cessation. Case reports of depression and suicide associated with isotretinoin use in Canada, Ireland, and France have also been published.[15-18]

A study of 94 US patients treated with isotretinoin for moderate to severe cystic acne in which patients were asked to note any unusual symptoms during treatment found that about 10% of patients reported insomnia and minor depression.[19] Middlecoop[20] documented significantly larger numbers of psychiatric adverse events, suicides, suicide attempts, and suicidal ideation reported worldwide with isotretinoin than with antibiotics used for acne treatment.

On the other hand, evidence exists that suggests there is no causal association between isotretinoin and depression. The predicted number of suicides in isotretinoin users treated over the 18-year period since marketing was calculated using the 1998 US rate of suicides of 11.4/100,000 for persons 15 to 24 years old[21] and an estimated number of 5 million exposed isotretinoin users.[22] This calculation yielded a predicted number of more than 400 suicides—considerably more than the 37 reported. However, this analysis is limited by possible substantial underreporting of suicides to the FDA and the unknown rate of suicide in persons with acne. Compared with other drugs in the FDA's database, isotretinoin has a large number of reports of depression and suicide attempt, and data mining analysis of adverse event and drug combinations has indicated a greater than expected number of suicides with isotretinoin use. The number of reports received after the 1998 product label warning suggests that this regulatory action may have resulted in increased reporting of depression and suicide with isotretinoin than with other drugs; however, this would not explain the reports received before 1998 that prompted the regulatory change.

An association between isotretinoin and depression may be due to a possible association between acne and depression. Anecdotal reports and studies suggest a relationship between skin disorders and decreased self-esteem, anxiety, depression, and suicide[23-27]; however, these studies have generally been small, uncontrolled, and have lacked the ability to examine the role of dermatologic treatment in the etiology of depression. In addition, the purported relationship between acne and depression would not fully explain the link between isotretinoin and depression since a positive disposition would be expected after efficacious isotretinoin treatment.

The reports of isotretinoin and depression could be due to factors coincidental with drug use. A substantial proportion of cases had previous psychiatric histories and other possible contributing factors (eg, personal relationship problems, stressful life events, alcohol use) besides their skin disorders and isotretinoin use. Depression is a multifactorial disorder, and both acne and psychiatric disorders[28,29] often affect persons in the 15- to 24-year age group. Because our analysis of case reports lacks the scientific rigor of a controlled clinical trial, we are unable to determine whether the association between isotretinoin and depression is causal. Nor are we able to assess the effect of different isotretinoin doses, accompanying physical side effects, and the role of possible contributing factors (such as personal relationship problems and alcohol use). Nevertheless, we do not believe that the reports of depression (including those with positive rechallenge) and suicide in persons prescribed isotretinoin should be dismissed.

A historical cohort epidemiologic study sponsored by the manufacturer of isotretinoin[30] showed no increased risk of depression and suicide attempts and suicide in isotretinoin users compared with a control group of antibiotic users treated for acne, but there were several important limitations of this study. These included a sample size that was too small for a study of suicide; probable underascertainment of psychiatric disorders since diagnosis codes (and not psychiatric drug prescriptions or interviews) were used to define cases; underascertainment of suicides because death certificates were not included as a source of data; lack of data on acne severity and dose and duration of treatment; and lack of generalizability to the United States of results obtained in the United Kingdom and Canada. In the United Kingdom and Canada, recommended doses of isotretinoin are lower, and in the United Kingdom, the drug is available to hospitals only and is prescribed by dermatologists or under the supervision of consultant dermatologists.[31]

Because of the continuing receipt of reports of depression and suicide and concern about the nearly 2000 pregnancy exposures[32] in US patients treated with isotretinoin, the FDA requested guidance from their Dermatologic and Ophthalmic Drugs Advisory Committee in September 2000 concerning risk management of isotretinoin. The Committee recommended that additional information be made available on depression and suicide through informed consent of patients (and parents or guardians if the patient is <18 years old) and a Medication Guide required to be given to patients with each dispensing. They also recommended studies to attempt to determine incidence and origin of depression in patients prescribed isotretinoin.

We agree that additional studies are needed to determine whether isotretinoin causes depression and to identify susceptible persons. In the meantime, physicians should be vigilant for symptoms of depression in patients treated with isotretinoin. They should advise patients (and parents/guardians,

if appropriate) to immediately report mood swings and symptoms suggestive of depression such as sadness and crying, loss of appetite, unusual fatigue, withdrawal, and inability to concentrate so that patients can be promptly evaluated for appropriate treatment, including consideration of drug discontinuation and referral for psychiatric care.

Several persons at the FDA have been involved over time in the analysis and interpretation of psychiatric case reports with isotretinoin exposure, including Kathryn O'Connell, MD, Jonathan Wilkin, MD, Amarilys Vega, MD, Roger Goetsch, RPh, MPH, David Graham, MD, Anne Trontell, MD, Claudia Karwoski, PharmD, and Erick Turner, MD. We acknowledge the assistance of Ana Szarfman, MD, PhD, for data mining analyses. We also thank physicians, pharmacists, patients and their families, and other reporters for submitting adverse event reports to the pharmaceutical manufacturer and the FDA.

REFERENCES

1. Wysowski DK, Pitts M, Beitz J. Depression and suicide in patients treated with isotretinoin. N Engl J Med 2001;344:460.
2. Szarfman A. Data mining of adverse events for Accutane/Roaccutane. Rockville (MD): Food and Drug Administration; 2000.
3. O'Neill RT, Szarfman A. Discussion: Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System by William DuMouchel (invited paper). The American Statistician 1999;53:190-6.
4. Restak RM. Pseudotumor cerebri, psychosis, and hypervitaminosis A. J Nerv Ment Dis 1972;155:72-5.
5. Feldman MH, Schlezinger NS. Benign intracranial hypertension associated with hypervitaminosis A. Arch Neurol 1970;22:1-7.
6. Henderson CA, Highet AS. Depression induced by etretinate. Br Med J 1989;298:964.
7. Logan RA. Efficacy of etretinate for the PUVA-dependent psoriatic. Clin Exp Dermatol 1987;12:98-102.
8. Borbujo Martinez JM, Casado Jimenez M, Garijo Lopez MB, Soto Melo J. Etretinate. Depression and behavioral changes: case report. Reactions 28 May 1988 No. 203, 7.
9. Zetterstrom RH, Simon A, Giacobini MMJ, Eriksson U, Olson L. Localization of cellular retinoid-binding proteins suggests specific roles for retinoids in the adult central nervous system. Neuroscience 1994;62:899-918.
10. Zetterstrom RH, Lindqvist E, Mata de Urquiza A, Tomac A, Eriksson U, Perlmann T, Olson L. Eur J Neurosci 1999;11:407-16.
11. LeDoze F, Debruyne D, Albessard F, Barre L, Defer GL. Pharmacokinetics of all-trans retinoic acid, 13-cis retinoic acid, and fenretinide in plasma and brain of rat. Drug Metab Dispos 2000;28:205-8.
12. Krezel W, Ghyselinck N, Samad TA, Dupe V, Kastner P, Borrelli E, et al. Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. Science 1998;279:863-7.
13. Hazen PG, Carney JF, Walker AE, Stewart JJ. Depression: a side effect of 13-*cis*-retinoic acid therapy. J Am Acad Dermatol 1983;9:278-9.
14. Scheinman PL, Peck GL, Rubinow DR, DiGiovanna JJ, Abangan DL, Ravin PD. Acute depression from isotretinoin [letter]. J Am Acad Dermatol 1990;22:1112-4.
15. Byrne A, Hnatko G. Depression associated with isotretinoin therapy [letter]. Can J Psychiatry 1995;40:567.
16. Byrne A, Costello M, Greene E, Zibin T. Isotretinoin therapy and depression—evidence for an association. Ir J Psych Med 1998; 15:58-60.
17. Bravard P, Krug M, Reznick JC. Isotretinoin and depression: care is needed. Nouv Dermatol 1993;12:215.
18. Duke EE, Guenther L. Psychiatric reactions to retinoids. Can J Dermatol 1993;5:467.
19. Bruno NP, Beacham BE, Burnett JW. Adverse effects of isotretinoin therapy. Cutis 1984;33:484-9.
20. Middlecoop T. Roaccutane (isotretinoin) and the risk of suicide: case report and a review of the literature and pharmocovigilance reports. J Pharm Pract 1999;12:374-8.
21. Hoyert DL, Kochanek KD, Murphy SL. Deaths: final data for 1997. National Vital Stat Rep vol 47, No. 19. Hyattsville (MD): National Center for Health Statistics; 1999.
22. Nelson R. Pharmacoepidemiologic analysis of Accutane-associated psychiatric events. Presentation for Hoffman-La Roche at FDA's Dermatologic and Ophthalmic Drugs Advisory Committee meeting, Gaithersburg, Md, Sept 19, 2000.
23. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, and atopic dermatitis and psoriasis. Br J Dermatol 1998;139:846-50.
24. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. Br J Dermatol 1997;137:246-50.
25. Niemeier V, Kupfer J, Demmelbauer-Ebner M, Stangier U, Effendy I, Gieler U. Coping with acne vulgaris. Dermatology 1998;196:108-15.
26. Kellet SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 1999;140:273-82.
27. Chu A, Cunliffe WJ. The inter-relationship between isotretinoin/acne and depression. J Eur Acad Dermatol Venereol 1999;12: 263.
28. Reinherz HZ, Giaconia RM, Lefkowitz ES, Pakiz B, Frost AK. Prevalence of psychiatric disorders in a community population of older adolescents. J Am Acad Child Adolesc Psychiatry 1993;32:369-77.
29. Garrison CZ, Waller JL, Cuffe SP, McKeown RE, Addy CL, Jackson KL. Incidence of major depressive disorder and dysthymia in young adolescents. J Am Acad Child Adolesc Psychiatry 1997: 36:458-65.
30. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. Arch Dermatol 2000;136:1231-6.
31. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. Br J Dermatol 1993;129:292-6.
32. Lyons Jones K, Adams J, Chambers CD, Erickson JD, Lammer E, Polifka J. Isotretinoin and pregnancy. JAMA 2001;285:2079.